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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,744	LE PAGE ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1,7-9 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11701,11901& 81605*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence alignment report (1)*.

DETAILED ACTION

Preliminary Amendment

1) Acknowledgment is made of Applicants' amendment filed 01/11/05. With this, Applicants have amended the specification.

Election

2) Acknowledgment is made of Applicants' election filed 02/04/03 and 09/30/04 in response to the restriction requirement mailed 12/04/02. Applicants have elected, with traverse, invention 2, claims 2, 6 and 10, drawn to the protein having the amino acid sequence of SEQ ID NO: 26. Applicants' traversal is on the following grounds: (a) According to M.P.E.P. § 803, if the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to independent or distinct inventions. (b) In the instant case, an examination of claims directed to nucleotide sequences, protein sequences encoded by the same nucleotide sequences, and antibodies that bind to the recited protein sequences, does not present a search creating an undue burden on the Examiner. (c) The art can be searched for nucleic acids, proteins and polypeptides encoded by those nucleic acids, and antibodies that bind to the proteins, as each of these groups is related to the other by the nature of the invention. Therefore, a search of one of these restricted inventions will often result in references disclosing the other inventions as well. For example, it is common in scientific publications disclosing novel expressed nucleotide sequences to additionally disclose the corresponding amino acid sequences), as well as antibodies that bind to those amino acid sequences, for example for protein purification purposes. (d) Applicants' traversal is further supported by a review of the International Search Report for International Application Number PCT 176899/02452. The instant application was filed as a 'Continuation' application of International Application Number PCT/GB99/02452. The International Search Report identities multiple inventions in the international application. However, a review of the inventions 1-87 reveals that each of these inventions is characterized by nucleotide sequences, protein and polypeptide sequences encoded by those nucleotide sequences and antibodies directed to said protein or polypeptides, among others. (e) A lack of unity of invention was not found between a *Streptococcus pneumoniae* protein or polypeptide having a sequence as depicted in SEQ ID NO.

2, a nucleic acid molecule encoding for the same or a homologue, derivative or fragment of said protein or polypeptide, and an antibody to said protein or polypeptide. Instead, a lack of Unity was found between each of inventions 1-87 as well as the subject matter of claim 20. (f) Under PCT Rule 13.2, Unity of Invention shall be fulfilled between a group of claimed inventions when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features (Patent Cooperation Treaty, Rule 13). (g) The special technical relationship between a DNA sequence and a protein or polypeptide sequence encoded by the same DNA sequence is such that a search of these restricted inventions does not create an undue burden on the Examiner. It is a matter of routine to deduce a protein sequence encoded by a DNA sequence once the DNA sequence is known. Utilizing the DNA sequence, protein sequences available in databases can easily be searched using local alignment search tools such as BLAST. (h) Applicants assert that restriction between DNA sequences and proteins encoded by those DNA sequences does not impose an undue burden on the Examiner.

Applicants' arguments have been carefully considered, but are not persuasive. First, Applicants are reminded that the instant application is not a national stage entry under 35 U.S.C. 371, but is a continuation application of a PCT application. The special technical feature is irrelevant since lack of unity does not apply to the instant non-371 application. As set forth in the restriction requirement mailed 12/04/02, the restriction is based on 35 U.S.C. § 121. Inventions 1-3 are drawn to structurally distinct amino acid sequences, each requiring a separate and non-coextensive search. Inventions 4-6 pertain to structurally distinct nucleotide sequences, each requiring a separate and non-coextensive search. Inventions 7-9 are drawn to antibodies with specificity for the structurally distinct amino acid sequences. The class/subclass to which inventions 1-3 belong are not the same class/subclass to which inventions 4-6 or inventions 7-9 belong. Clearly, these products require non-coextensive and burdensome searches in different classes and subclasses. Contrary to Applicants' argument, not all patent and non-patent publications disclose the corresponding deduced amino acid sequences of the disclosed nucleotide sequences and/or antibodies to such amino acid sequences. The polypeptide of inventions 1-3 and nucleic acid molecules of inventions 4-6 are patentably distinct inventions for the following reasons. Polypeptides, which are composed of amino acids, and nucleic acids, which are composed of purine and pyrimidine units, are structurally distinct molecules; any relationship

between a polynucleotide and polypeptide is dependent upon the information provided by the nucleic acid sequence open reading frame as it corresponds to the primary amino acid sequence of the encoded polypeptide. In the present claims, the nucleic acid molecule of inventions 4, 5 and 6 does not necessarily encode a polypeptide of inventions 1, 2 and 3. For example, as disclosed in the specification, SEQ ID NO: 26 is 279 amino acids in length, whereas the nucleic acid molecule of claim 8(v) requires only 3 or more nucleotides (which would encode a fragment, homologue, or derivative of SEQ ID NO: 26). Similarly, the nucleic acid molecule of claim 8(ii) is a complementary nucleotide sequence, and therefore would not encode the polypeptide of inventions 1-3. Furthermore, the information provided by the nucleic acid molecule of inventions 4-6 can be used to make a materially different polypeptide than that of inventions 1-3. For example, a complementary nucleic acid molecule encompasses molecules that contain point mutations, splice sites, frameshift mutations or stop codons, which would result in a different open reading frame, and thus encode a protein that lacks any significant structure in common with the polypeptide of inventions 1-3. In addition, while a polypeptide of inventions 1-3 can be made by methods using some, but not all, of the nucleic acid molecules that fall within the scope of inventions 4-6, it can also be recovered from a natural source using biochemical means. For instance, the polypeptide can be isolated using affinity chromatography. For these reasons, the inventions of groups 1-3 and 4-6 are patentably distinct.

Furthermore, searching the inventions of groups 1-3 and 4-6 together would impose a serious search burden. In the instant case, the search of the polypeptides and the nucleic acid molecules are not coextensive. The inventions 1-3 and 4-6 have a separate status in the art as shown by their different classifications. In cases such as this one where descriptive sequence information is provided, the sequences are searched in appropriate databases. There is search burden also in the non-patent literature. Prior to the concomitant isolation and expression of the sequence of interest there may be journal articles devoted solely to polypeptides which would not have described the polynucleotide. Similarly, there may have been "classical" genetics papers which had no knowledge of the polypeptide but spoke to the gene. Searching, therefore is not coextensive. In addition, the polypeptide claims include polypeptides having substantial identity to the sequence identified. This search requires an extensive analysis of the art retrieved in a sequence search and will require an in-depth analysis of technical literature. The scope of nucleic

acid molecules as claimed extend beyond the polynucleotides that encode the claimed polypeptides as explained above; furthermore, a search of the nucleic acid molecules of claim 8(ii) and 8(v) would require an oligonucleotide search, which is not likely to result in relevant art with respect to the polypeptide of groups 1-3. As such, it would be burdensome to search the inventions of groups 1-3 and 4-5 together.

The polypeptide of inventions 1-3 and the antibody of inventions 7-9 are patentably distinct for the following reasons. While both are polypeptides, in this instance, the polypeptide of inventions 1-3 is a single chain molecule that functions as a microbial antigen, whereas the polypeptide of inventions 7-9 encompasses antibodies including IgG which comprises 2 heavy and 2 light chains containing constant and variable regions, and including framework regions which act as a scaffold for the 6 complementarity determining regions (CDRs) that function to bind an epitope. Thus, the polypeptide of inventions 1-3 and the antibody of inventions 7-9 are structurally distinct molecules. Furthermore, searching the inventions 1-3 and inventions 7-9 would impose a serious search burden. The inventions have a separate status in the art as shown by their different classifications. A polypeptide, and an antibody which binds to the polypeptide, would require different searches. An amino acid sequence search of the full-length protein is necessary for a determination of novelty and unobviousness of the protein. However, such a search is not required to identify the antibodies of inventions 7-9. Furthermore, antibodies which bind to an epitope of a polypeptide of inventions 1-3 may be known even if the polypeptide of inventions 1-3 is novel. In addition, the technical literature search for the polypeptide of inventions 1-3 and the antibody of inventions 7-9 are not coextensive, e.g., antibodies may be characterized in the technical literature prior to discovery of sequence of their binding target.

The nucleic acid molecules of inventions 4-6 and the antibody of inventions 7-9 are patentably distinct for the following reasons. The antibody of inventions 7-9 includes, for example, IgG molecules which comprise 2 heavy and 2 light chains containing constant and variable regions, and including framework regions which act as a scaffold for the 6 complementarity determining regions (CDRs). The antibody of inventions 7-9 are structurally distinct molecules; any relationship between a nucleic acid molecule and polypeptide is dependent upon the information provided by the nucleic acid sequence open reading frame as it corresponds to the primary amino acid sequence of the encoded polypeptide. In the present claims, a nucleic acid molecule of

inventions 4-6 will not encode an antibody of inventions 7-9. The antibody of inventions 7-9 cannot be encoded by the nucleic acid molecule of inventions 4-6. Therefore the antibody and nucleic acid molecules are patentably distinct. The antibody and nucleic acid molecules have a separate status in the art as shown by their different classifications. Furthermore, searching the inventions of groups 7-9 and groups 4-6 would impose a serious search burden since a search of the nucleic acid molecules would not be used to determine the patentability of the antibodies of inventions 7-9, and vice-versa.

For reasons delineated above, the restriction requirement set forth previously is proper and is hereby made FINAL. However, since Applicants have elected claims directed to a product, if these product claims were subsequently found allowable, withdrawn process claims that depend from or otherwise included all the limitations of the allowable product claims, will be rejoined in accordance with the provisions of MPEP § 821.04. *Process claims that depend from or otherwise include all the limitations of the patentable product* will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. *Failure to do so may result in a loss of the right to rejoinder.* Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the Examiner before the patent issues. See MPEP § 804.01.

Status of Claims

3) Claims 1-20 are pending.

Claims 1, 7-9 and 13-20 are withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 2-6 and 10-12 are under examination. A First Action on the Merits is issued herein on these claims.

Sequence Listing

4) Acknowledgment is made of Applicants' submission of raw sequence listing and CRF, which have been entered on 09/23/05.

Information Disclosure Statements

5) Acknowledgment is made of Applicants' information disclosure statements filed 11/07/01, 11/09/01 and 08/16/05. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Priority

6) This application is a continuation of PCT/GB99/02452 filed 07/27/1999, which claims priority to the provisional application 60/125,329 filed 03/19/1999. This application claims foreign priority to 9816336.3, filed 07/27/1998 in the United Kingdom.

It is noted that on 09/30/05 Applicants have submitted a certified copy of the foreign priority document, 9816336.3, filed 07/27/1998 in the United Kingdom. Both the transmittal letter and the oath/declaration filed 01/26/01 however states that application 9816336.3 filed 07/27/1998 is a German patent application. Applicants should clarify this discrepancy in response to this Office Action.

Specification

7) The specification is objected to for the following reason:

The first paragraph of the specification lacks information of the prior/priority applications. Amendments to the first paragraph of the specification are suggested.

Rejection(s) under 35 U.S.C § 101

8) 35 U.S.C. § 101 states:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of

matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this cycle.

9) Claims 2, 4-6 and those that depend therefrom are rejected under 35 U.S.C § 101 as being directed to a non-statutory subject matter.

Claims 2 and 4-6 are drawn to a protein or polypeptide, or a homologue, derivative, or an antigenic or immunogenic fragment thereof, and therefore read on products of nature, i.e., a protein or polypeptide, or a homologue, derivative, or an antigenic or immunogenic fragment thereof, naturally occurring on the surface of *S. pneumoniae*. The claims lack limitations, which distinguish the products from those that may exist naturally. Consequently, the claims do not embody patentable subject matter as defined in 35 U.S.C § 101. See MPEP 2105. The rejection can be obviated by amending the claims to recite --An isolated-- in connection with the products to reflect the hands of the inventors in the production or creation of the recited product if such a recitation has descriptive support in the specification, as originally filed.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Written Description)

10) Claims 4, 5 and 10-12 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It is noted that the polypeptide which is 'substantially identical' to a polypeptide having the amino acid sequence of SEQ ID NO: 26, a 'homologue', 'derivative', or 'fragment' thereof as recited in the instant claims does not exist independent of its antigenic function, i.e., the ability to bind to antibody specific for *Streptococcus pneumoniae,* immunogenic function, i.e., the ability to elicit a *Streptococcus pneumoniae*-specific humoral and/or cell mediated immune response, and immunoprotective or vaccine function, i.e., the ability to confer immunoprotection against *Streptococcus pneumoniae* infection. The specification discloses diagnostic applications or vaccine intentions for the claimed polypeptide homologue, derivative, or fragment thereof. However, the instant specification fails to teach a single 'homologue, derivative, or fragment' of the amino acid sequence of SEQ ID NO: 26, or a polypeptide that is substantially identical to the polypeptide having the amino acid sequence of SEQ ID NO: 26, which concurrently has the *Pneumococcus*-specific antigenic, immunogenic, diagnostic, or immunoprotective ability.

Diagnostic or vaccine applications minimally require an ability to elicit a specific immune response or bind specifically to an antibody. The precise structure or relevant identifying characteristics of DNA molecules that encode a 'homologue, derivative, or fragment' of the amino acid sequence of SEQ ID NO: 26, or a polypeptide that is substantially identical to the polypeptide having the amino acid sequence of SEQ ID NO: 26 and having the specific binding, immunogenic, or prophylactic ability can only be determined empirically by actually making the DNA molecules that encode the polypeptide homologues, derivatives, or fragments, and testing varied DNA molecules to determine whether they encode the recited polypeptide homologues, derivatives, or fragments having the particularly disclosed specific binding, immunogenic, or prophylactic activity. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement that the invention includes a polypeptide substantially identical to the polypeptide of SEQ ID NO: 26, or a homologue, derivative or fragment of the polypeptide of SEQ ID NO: 26 is insufficient to meet the adequate written description requirement of the claimed invention. The polypeptide of SEQ ID NO: 26 has specific biologic properties dictated by the structure of the polypeptide and the corresponding structure of the structural gene sequence, which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the polypeptide homologue, derivative or fragment encoded, and the function of the encoded polypeptide homologue, derivative or fragment. The function cannot be predicted from the modification of the structure of the gene and in the instant case, the DNA encoding the recited polypeptide homologue, derivative or fragment. Applicants have not shown that variation or modification of a reference sequence encoding a reference polypeptide as claimed would automatically predict the production of a polypeptide homologue, derivative or fragment having the recited functional activity, i.e., *Streptococcus pneumoniae*-specific antigenic, immunogenic, diagnostic, or vaccine (prophylactic) ability. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of DNA molecules encoding a representative number of species of polypeptide homologues, derivatives, fragments or substantially identical polypeptides of SEQ ID NO: 26 as recited, sufficient to allow one skilled

in the art to determine that the inventors had possession of the invention as claimed. With the exception of a pneumococcal polypeptide of SEQ ID NO: 26, a skilled artisan cannot envision the detailed chemical structure of all the polypeptide homologue, derivative, fragment or substantially identical polypeptide species encompassed by the recited molecule. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is a part of the invention and a reference to a potential method of isolating it. The nucleic acid encoding the polypeptide variant or an immunogenic fragment itself is required. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.*

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

11) Claims 4, 5 and 10-12 are rejected under 35 U.S.C. § 112, first paragraph, because the specification while being enabling for an isolated or purified *Streptococcus pneumoniae* polypeptide having the amino acid sequence of SEQ ID NO: 26, and an antigenic or immunogenic composition comprising the polypeptide and an excipient, diluent, or adjuvant, does not reasonably provide enablement for a 'homologue or derivative' or 'fragments' of said polypeptide, and a protein or polypeptide 'substantially identical' thereto, and a 'vaccine' composition comprising the polypeptide of the amino acid sequence of SEQ ID NO: 26, a 'homologue', 'derivative', or 'fragment' thereof, and an immunogenic and/or antigenic composition or a diagnostic composition comprising a 'homologue', 'derivative', or 'fragment' of SEQ ID NO: 26, as recited broadly.

The instant claims are evaluated based on the *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

The enabling disclosure in the instant specification is limited to an isolated or purified

279 amino acid-long *Streptococcus pneumoniae* polypeptide having the amino acid sequence of SEQ ID NO: 26, and an antigenic or immunogenic composition comprising the polypeptide and an excipient, diluent, or adjuvant. A composition comprising such a long pneumococcal polypeptide is expected to serve as an immunogenic or antigenic composition. However, a 'homologue', 'derivative', or 'fragments' of the pneumococcal polypeptide of SEQ ID NO: 26 is not shown to serve as an antigenic/immunogenic composition, a vaccine, or a diagnostic composition. A vaccine 'must by definition trigger an immunoprotective response in the host vaccinated; mere antigenic response is not enough'. *In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).* In the instant case, the active element in the vaccine or diagnostic composition is the protein or the polypeptide of the amino acid sequence, SEQ ID NO: 26, which is required to be 'immunoprotective' against a pneumococcal infection. *S. pneumoniae* is known in the art to encompass multiple serotypes. A review of the instant specification indicates a lack of enabling disclosure for a 'vaccine' or 'diagnostic' composition that comprises the isolated or purified polypeptide of SEQ ID NO: 26, a 'homologue', 'derivative', or 'fragment' thereof which protected a susceptible host against *S. pneumoniae* infection, or reduced morbidity and mortality due to *S. pneumoniae* infections, or diagnosed a pneumococcal infection in a host. The precise structure or amino acid composition of the 'homologue', 'derivative', or 'fragment' of the polypeptide of SEQ ID NO: 26 is not disclosed. There is no showing that the claimed polypeptide of SEQ ID NO: 26, let alone its 'homologue', 'derivative', or 'fragment', elicited a humoral and/or cell mediated protective immune response in a suitable host who is susceptible against pathogens that produce or carry such element. This is critically important because it is well known in the art that, of a myriad of polypeptides that may be produced by a bacterial or microbial pathogen, not all polypeptides elicit a pathogen-specific immune response that is protective against the pathogen. The art of vaccines recognizes the unpredictability associated with whether or not an antigen or immunogenic component derived from a microbial pathogen is immunoprotective. For instance, Ellis RW (*Vaccines*, (Eds) Plotkin *et al.*, W.B. Saunders Company, Philadelphia, Chapter 29, 568-575, 1988, see page 571, second full paragraph) reflected this problem in the teaching that the key to the problem of vaccine development "is the identification of that protein component of a ..... microbial pathogen that itself can elicit the production of protective antibodies ..... and thus protect the

host against attack by the pathogen". It is emphasized that predictability or unpredictability is one of the *Wands* factors for enablement. In the instant case, the claimed protein or polypeptide, in isolated, purified or substantially purified form, is not evaluated for its protective capacity against *S. pneumoniae* infections using an art-accepted *in vivo* animal model, nor are there any *in vitro* test results correlative of protection against infections by homologous or heterologous strains of *S. pneumoniae*. A 'homologue', 'derivative', or 'fragment' of SEQ ID NO: 26 of any size having the ability to immunoprotect against homologous or heterologous pneumococcus strain is simply not enabled within the instant specification. This is important because the ability of a microbial polypeptide 'homologue', 'derivative', or 'fragment' obtained from one serotype of that microbe to confer a broad genus-wide, species-wide, or serotype-wide protection is not predictable. There is no evidence within the instant specification that the protein or polypeptide of SEQ ID NO: 26 is produced by all serotypes of *S. pneumoniae*, and that it confers immunoprotection against homologous and heterologous serotypes of *S. pneumoniae*. The evidence in the specification is clearly not commensurate in scope with the breadth of the claim(s). The ability of the claimed protein or polypeptide, or its homologue, derivative or fragment to reduce morbidity and mortality due to infections by homologous or heterologous pneumococcal strain or by all 23 serotypes of pneumococcus is not a predictable, since different strains or serotypes of *S. pneumoniae* may produce heterogeneous or structurally variable polypeptides. The term 'homologue' or 'derivative' encompasses innumerable 'variants' of the polypeptide of SEQ ID NO: 26 having any amino acid substitution, deletion, or insertion. A random replacement affecting the epitopic amino acid positions that are critical, for example, to the three-dimensional conformational structure and specific binding property of the protein or polypeptide, would result in a protein or polypeptide that may be non-functional, or not optimally antigenic as a diagnostic reagent, or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (*Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could

> create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool.

Thus, the art reflects that variations in critical residues at specific positions in an amino acid sequence could result in a protein or polypeptide, which may induce an antibody that may not recognize or bind to the native protein of a microorganism. Given the art-known fact that a change in a single amino acid residue dramatically changes the biological activity of a protein, one cannot predict that the claimed protein or a fragment thereof would have the ability to reduce colonization by any serotype or all serotypes of *S. pneumoniae*. Absent a concrete showing that the protein/polypeptide or its fragments, homologues, or derivatives as claimed are produced by all serotypes of *Streptococcus pneumoniae*, and that they reduce colonization by homologous and heterologous serotypes of *S. pneumoniae*, instant claims are viewed as being non-enabled with respect to the full scope. Clearly, the specification lacks adequate guidance and disclosure that would limit the experimentation from being undue. Given the art-recognized unpredictability associated with the immunoprotective or diagnostic capacity of a microbial polypeptide, structurally heterogeneous homologues, derivatives, or fragments thereof, one of skill in the art would look into the specification for specific teaching and guidance, which in the instant case is lacking. Due to the lack of specific guidance and disclosure as to the precise structure of the polypeptide homologues, derivatives, or fragments that have the immunoprotecive or diagnostic ability to immunoprotect against or diagnose infections due to any serotype of penumococcus; the lack of working examples enabling the full scope of the claims; the art-recognized unpredictability factor; the breadth of the claims; and the quantity of experimentation necessary, undue experimentation would have been required to practice the invention as claimed. *Ex parte Foreman*, 230 USPO 546, 547 (*Bd. Pat. Appeals. and Inter.* 1986). The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C. § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

12) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

13) Claims 2-6 and 10-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

Applicants regard as the invention.

(a) Claim 5 is vague and indefinite in the limitation: 'homologue' or 'derivative', because it is unclear what is encompassed in this limitation. What constitutes a 'fragment or variant', and how much of the promoter's original structure has to be retained such that the resulting product can be considered a 'fragment or variant' is not clear. The metes and bounds of the structure encompassed in the limitation 'fragment or variant' are indeterminate.

(b) Analogous criticism applies to claim 10.

(c) Claim 10 is vague and indefinite in the limitation: 'fragments'. What constitutes 'fragments', and how much of the protein's or polypeptide's original structure has to be retained such that the resulting products can be considered 'fragments' is not clear. The metes and bounds of the structure encompassed in the limitation 'fragments' are indeterminate.

(d) Claims 2 and 10 are vague and indefinite in the recitation: 'a sequence..... shown in Table .....' without distinctly reciting that the sequence is --the amino acid sequence--.

(e) Claims 2, 6 and 10 are indefinite in the limitation 'shown in table 2'; 'defined in Tables ...'; and 'shown in Tables ...' respectviley, because the limitation fails to point out what is included or excluded by the claim language. M.P.E.P 2173.05(s) states that where possible, claims are to be complete in themselves. Incorporation by reference to Tables and Figures, or Examples as in this case, is a necessity doctrine, not for Applicants' convenience. See *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993).

(f) Claim 4 is vague and indefinite in the limitation: 'substantially pure form', because it is unclear what degree of purity is encompassed in this limitation.

(g) Claim 3 is vague and indefinite in the limitation: 'substantially identical', because it is unclear what degree of identity is encompassed in this limitation.

(h) Claims 4 and 5 are vague and indefinite in the limitation: 'defined in any one of ...'. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation with --claimed in any one of ....--.

(i) Claims 3-6 and 10 are vague and confusing because it is unclear how the limitation 'protein' differs in scope from the recited 'polypeptide'. It is suggested that Applicants retain one terminology.

(j) Claims 3-6, 11 and 12, which depend directly or indirectly from claim 1 or claim 10, are also rejected because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

14) The following is a quotation of the appropriate paragraph(s) of 35 U.S.C. § 102 that form the basis for the rejection(s) under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(e)** the invention was described in-
> **(2)** a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

15) Claims 4-6 and 10-12 are rejected under 35 U.S.C § 102(e)(2) as being anticipated by Doucette-Stamm *et al.* (US 6,800,744, filed 07/02/1997) ('744).

The term 'vaccine' is viewed as representing the intended use of the claimed product and therefore is not given any patentable weight. It is noted that the 'homologue' or 'derivative' claimed in claims 5 and 10; the 'fragments' recited in claim 10; and the 'substantially identical' protein or polypeptide claimed in claim 4, lack a structure or size limit.

Doucette-Stamm *et al.* ('744) disclosed a polypeptide or protein comprising the amino acid sequence (Accession ADR96203) that is 99.9% identical to the instantly claimed protein or polypeptide comprising the amino acid sequence of SEQ ID NO: 26. See the attached sequence alignment report. A vaccine (i.e., immunogenic) composition comprising an adjuvant and said protein or polypeptide for eradication of *S. pneumoniae* infection is taught. See columns 39 and 40. The polypeptide is useful in diagnosis and therapy of pathological conditions (see abstract). The polypeptide is in a substantially pure form (see lines 12-15 in column 5). The prior art protein or polypeptide is viewed as a protein or polypeptide, which is substantially identical to SEQ ID NO: 26, or a homologue or derivative of SEQ ID NO: 26.

Claims 4-6 and 10-12 are anticipated by Doucette-Stamm *et al.* ('744).

Objection(s)

16) Claims 2-6 and 10-12 are objected to for including non-elected subject matter.

Remarks

17) Claims 2-6 and 10-12 stand rejected.

18) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions

24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (571) 273-8300.

19) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

20) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

November, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER

SEQ ID NO,26

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RESULT 5
ADR96203
ID   ADR96203 standard; protein; 280 AA.
XX
AC   ADR96203;
XX
DT   16-DEC-2004  (first entry)
XX
DE   Novel S. pneumoniae protein sequence, SEQ ID 4838.
XX
KW   Meningitis; bacteraemia; pneumonia; otitis media; vaccine;
KW   bacterial infection.
XX
OS   Streptococcus pneumoniae.
XX
PN   US6800744-B1.
XX
PD   05-OCT-2004.
XX
PF   30-JUN-1998;   98US-00107433.
XX
PR   02-JUL-1997;   97US-0051553P.
PR   12-MAY-1998;   98US-0085131P.
XX
PA   (GENO-) GENOME THERAPEUTICS CORP.
XX
PI   Doucette-Stamm LA,  Bush D;
XX
DR   WPI; 2004-697205/68.
DR   N-PSDB; ADR93600.
XX
PT   New isolated nucleic acid encoding a Streptococcus pneumoniae
PT   polypeptide, useful for diagnosing, preventing and/or treating
PT   pathological conditions resulting from the bacterial infection.
XX
PS   Disclosure; SEQ ID NO 4838; 151pp; English.
XX
CC   The invention relates to an isolated nucleic acid comprising a sequence
CC   encoding a Streptococcus pneumoniae ADR91366polypeptide, or its
CC   fragments, with any of 9 fully defined sequences (appearing as ADR94308,
CC   ADR94489, ADR94800, ADR94837, ADR94969, ADR95253, ADR95642, ADR95682,
CC   ADR96079) or any of the fully defined sequences appearing as ADR91705,
CC   ADR91886, ADR92197, ADR92234, ADR93039, ADR93079, ADR92366, ADR92650 or
CC   ADR93476 or at least 20 or 30 consecutive nucleotides of the nucleotide
CC   sequences, or at least 40, 60 or 300 consecutive nucleotides, which is
CC   hybridisable under high stringency conditions to the nucleotide sequence.
CC   The nucleic acids and proteins are chosen from 5206 disclosed sequences.
CC   Also included are a recombinant expression vector comprising the isolated
CC   nucleic acid cited above operably linked to a transcription regulatory
CC   element, a cell comprising the recombinant expression vector and a probe
CC   comprising at least 20 consecutive nucleotides of the nucleotide
CC   sequences as cited above. The methods and compositions of the present
CC   invention are useful for the diagnosis, prevention and/or treatment of
CC   pathological conditions resulting from bacterial infection by
CC   Streptococcus pneumoniae e.g. pneumonia, bacteraemia, meningitis and
CC   otitis media. The present sequence is one of the 2603 disclosed S.
CC   pneumoniae protein sequences. Note: The sequence data for this patent did
CC   not form part of the printed specification, but was obtained in
CC   electronic format directly from USPTO at
CC   seqdata.uspto.gov/sequence.html?DocID=6800744B1.
XX
SQ   Sequence 280 AA;

  Query Match             99.9%;  Score 1386;  DB 8;  Length 280;
  Best Local Similarity   99.6%;  Pred. No. 7.3e-125;
  Matches  278;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MGIALENVNFTYQEGTPLASAALSDVSLTIEDGSYTALIGHTGSGKSTILQLLNGLLVPS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          2 MGIALENVNFTYQEGTPLASAALSDVSLTIEDGSYTALIGHTGSGKSTILQLLNGLLVPS 61

Qy         61 QGSVRVFDTLITSTSKNKDIRQIRKQVGLVFQFAENQIFEETVLKDVAFGPQNFGVSEED 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         62 QGSVRVFDTLITSTSKNKDIRQIRKQVGLVFQFAENQIFEETVLKDVAFGPQNFGVSEED 121

Qy        121 AVKTAREKLALVGIDESLFDRSPFELSGGQMRRVAIAGILAMEPAILVLDEPTAGLDPLG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        122 AVKTAREKLALVGIDESLFDRSPFELSGGQMRRVAIAGILAMEPAILVLDEPTAGLDPLG 181

Qy        181 RKELMTLFKKLHQSGMTIVLVTHLMDDVAEYANQVYVMEKGRLVKGGKPSDVFQDVVFME 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        182 RKELMTLFKKLHQSGMTIVLVTHLMDDVAEYANQVYVMEKGRLVKGGKPSDVFQDVVFME 241

Qy        241 EVQLGVPKITAFCKRLADRGVSFKRLPIKIEEFKESLNG 279
              |||||||||||||||||||||||:||||||||||
Db        242 EVQLGVPKITAFCKRLADRGVSFKRLPVKIEEFKESLNG 280
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